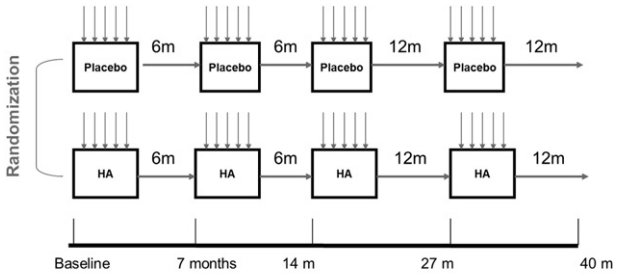

Figure 1. Study design.

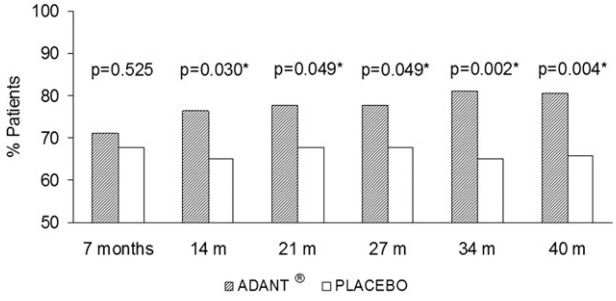

Figure 2. Evolution of % responders through the study (OMERACT-OARSI 2004) in mITT population.

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PREVENTION OF KNEE OSTEOARTHRITIS IN OVERWEIGHT FEMALES; THE FIRST PREVENTIVE RANDOMIZED CONTROLLED TRIAL

J. Runhaar [1], M. van Middelkoop [1], D. Vroegindeweij [2], E.H. Oei [1], M. Reijman [1], G.J. van Osch [1], B.W. Koes [1], S.M. Bierma-Zeinstra [1]. [1] *Erasmus MC, Rotterdam, Netherlands;* [2] *Maasstad Hosp., Rotterdam, Netherlands*

Purpose: With increasing rates of obesity, continued aging of the population and a lack of available disease modifying interventions for osteoarthritis (OA), primary prevention of OA is of great significance. Obesity is known to be one of few modifiable risk factors for incident knee OA. The purpose of the present study was to evaluate the effect of a pragmatic tailor made weight reduction program and of oral glucosamine sulphate (double blind; placebo-controlled), in a factorial design, on the incidence of knee OA over 2.5 years of follow-up in overweight, middle-aged females; free of clinical and radiological knee OA at baseline (ISRCTN 42823086). Worldwide, this is the first large RCT on prevention of knee OA. Here we present the effects of the weight reduction program.
Methods: 50 general practitioners in the area of Rotterdam, the Netherlands, contacted all women between 50 and 60 years registered at their practice (6691 women). All women with a self reported BMI $\geq$ 27 interested to participate in the study (889 women) were screened on the inclusion criteria. Subjects had to be free of knee OA according to the ACR criteria, free of contraindications to MRI, free of rheumatic diseases and not using oral glucosamine during the past 6 months. In total, 407 women met all inclusion criteria, were invited for baseline measurements and were randomized. Based on baseline standardized semi-flexed X-rays, all knees with a K&L-grade of $\geq$ 2 were excluded. Half of all women were randomized into the control group (CG) and received no intervention on weight reduction. The other half was assigned to the weight reduction group (WRG) and was referred to a local dietician for guidance on nutrition and physical activity behaviours based on Motivational Interviewing. In addition, they were invited to join a physical activity class of 20 weekly group lessons, guided by a physical therapist. Every 6 months, all 407 subjects received a home visit to measure body weight, replace study medication and check their well-being. Pre-specified primary outcome measure was incidence of knee OA, defined by incidence of either K&L-grade $\geq$ 2, joint space narrowing of $\geq$ 1.0 mm or clinical knee OA according to the ACR criteria.
Results: At baseline, subjects were 55.7 $\pm$ 3.2 years old, had a mean body weight of 88.7 $\pm$ 13.2 kg and a mean BMI of 32.4 $\pm$ 4.3 kg/m2; equally spread over both groups. All 2.5 year follow-up measurements have been completed (10% lost to follow-up). Almost 75% of WRG attended the physical activity class at least once (0 to 21 lessons; 7 on average). Ninety percent visited the dietician at least once (0 to 32 visits; 6 on average). After 2.5 years and on all intermediary measurements, body weight was not significantly different between WRG and CG. However at 6 months follow-up (during highest intensity of the interventions), WRG had a significantly larger reduction in body weight than CG (-0.9 kg in WRG vs +0.9 kg in CG, $p < 0.00$), and a significant larger part of WRG (12%) fulfilled the pre-specified objective of 5 kg or 5% weight reduction than in CG (6%, $p = 0.04$). After 2.5 years, subjects compliant to the weight reduction intervention ($\geq$6 visits and $\geq$7 lessons) showed a mean weight reduction of 1.4 $\pm$ 5.5 kg, compared 0.1 $\pm$ 6.3 kg in the controls ($p = 0.22$). Up to now, only 50% of the primary outcome measure has been scored. Based on these data, in the present population incidence of knee OA was 19%. To avoid publication of unfounded study results, no interim analyses on the primary outcome measure were performed. All primary outcomes will be available in February 2012 and will be presented at the Congress.
Conclusions: The pragmatic tailor made intervention did not show effects on body weight throughout the 2.5 years follow-up, but several measures of weight reduction showed a significant effect in favour of WRG within the first 6 months. Sample size calculations were based on a 20% incidence in the control group, 10% incidence in the intervention group and 20% lost to follow-up. So far, incidence number reached expected levels and percentage lost to follow-up was considerably lower than expected. Final results will be available at the OARSI World Congress.

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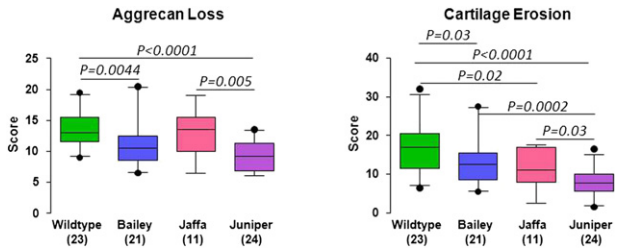
CARTILAGE LOSS DURING SYMPTOMATIC MAINTENANCE AFTER A CLINICALLY SIGNIFICANT WEIGHT LOSS IN OBESE OSTEOARTHRITIS PATIENTS: A RANDOMIZED CONTROLLED TRIAL

M. Henriksen [1], R. Christensen [1,2], D.J. Hunter [3], E. Dam [4], S. Lohmander [2,5], M. Boesen [1,6], H. Gudbergsen [1], H. Bliddal [1]. [1] *The Parker Inst., Copenhagen, Denmark;* [2] *Univ. of Southern Denmark, Odense, Denmark;* [3] *Univ. of Sydney, Sydney, Australia;* [4] *Biomediq, Copenhagen, Denmark;* [5] *Univ. of Lund, Lund, Sweden;* [6] *Dept. of Radiology, Frederiksberg Hosp., Copenhagen, Denmark*

Purpose: Weight loss in overweight patients with knee osteoarthritis (OA) is recommended because it effectively induces symptomatic relief. However, maintaining weight loss and symptomatic relief is a challenge, and the effects of weight and symptom maintenance programs on cartilage deterioration are unknown. The purpose of this study was to compare cartilage loss in the knee joint over 1-year of dietary consultancy or therapeutic exercise vs. control in obese knee OA patients after a clinically significant weight loss.
Methods: Obese individuals (>50 years) with knee OA (ACR criteria), and motivated for weight loss, were enrolled in a 16-week weight loss program that induced a clinically significant weight loss (>10%). They were then randomized to either 1-year maintenance program with [D] continuous dietary consultations, or [E] knee exercise program supervised by a physical therapist or [C] a control group receiving no support from the study team for 1 year. The primary endpoint was annual change in total knee joint cartilage volume assessed by MRI. Secondary outcomes included changes in the individual regional cartilage volumes assessed by automatic segmentation of MRI and changes in average knee symptoms measured as the mean of 4 out of the 5 KOOS subscales (excluding sports and recreation subscale) over 1 year. The outcomes were analyzed statistically using ANCOVA with a factor for maintenance group, adjusting for the level at baseline.
Results: 192 participants, mean age 63 years (SD 6), mean weight 103.2 kg (15.0), and BMI of 37.3 (4.8) were randomized (1:1:1; 64 patients in each group). The average annual loss in total cartilage volume across groups was 1,150 mm^3. There were no statistically significant group differences in changes in cartilage volumes at the 1 year follow-up (Table). The average symptoms deteriorated by 8.4 points (SE 1.1) across groups. There were also no statistically significant group differences for the average symptoms (KOOS) or any of the other secondary outcomes. Ancillary analysis showed that the annual changes in total cartilage volume were not associated with annual changes in average symptoms (r=-0.007, P=0.93).
Conclusion: This study showed no differences in knee joint cartilage loss between obese knee OA patients who after a significant weight loss



participated in either dietary maintenance, knee exercise or a control group for 1 year. The cartilage loss was not associated with changes in symptoms.Trial registration: {NCT00655941}

ANCOVA results for changes in weight, BMI and cartilage volumes (mm3) and average symptoms (KOOS)

	Group C		Group D		Group E		*ANCOVA*
	Mean	95% CI	Mean	95% CI	Mean	95% CI	*P-value*
Weight, kg	-9.8	-11.7 to -7.8	-12.8	-14.7 to -11.0	-8.0	-9.9 to -6.1	0.0018
BMI	-3.5	-4.2 to -2.8	-4.6	-5.3 to -4.0	-2.9	-3.6 to -2.2	0.0023
Cartilage Volume (mm^3)							
Total knee	-1219	-1378 to -1061	-1119	-1273 to -965	-1112	-1275 to -949	0.5770
Lateral Femoral	-251	-284 to -219	-227	-259 to -196	-236	-270 to -203	0.5755
Medial Femoral	-319	-363 to -275	-269	-311 to -226	-285	-330 to -340	0.2651
Patellar	-214	-261 to -167	-202	-247 to -156	-167	-215 to -119	0.3595
Lateral Tibial	-265	-331 to -199	-246	-309 to -182	-279	-347 to -211	0.7745
Medial Tibial	-172	-238 to -107	-173	-237 to -110	-146	-214 to 78	0.8099
Average Symptoms (KOOS)	8.3	4.6 to 11.9	9.0	5.5 to 12.6	7.8	4.1 to 11.4	0.8843

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BLOCKING COLLAGENOLYSIS PREVENTS AGGRECAN LOSS MORE EFFECTIVELY THAN BLOCKING AGGRECANOLYSIS IN THE AGGRECAN INTERGLOBULAR DOMAIN, IN VITRO AND IN VIVO

S.J. Gauci [1], C.B. Little [2], A.J. Fosang [3]. [1] *Murdoch Childrens Res. Inst., VIC, Australia;* [2] *Raymond Purves Bone & Joint Res. Labs, Univ. of Sydney, NSW, Australia;* [3] *Univ. of Melbourne & Murdoch Childrens Res. Inst., VIC, Australia*

Purpose: We have compared knockin mice with aggrecan and type II collagen resistant to aggrecanases, collagenases, or both families of enzymes, to identify the most important proteolytic driver for cartilage erosion. Specifically, the cleavage site in the aggrecan interglobular domain (IGD) of Jaffa is changed from $E^{373}\downarrow{}^{374}$ALG to $E^{373}\downarrow{}^{374}$NVY and the collagenase cleavage site in the α1(II) chain of Bailey is changed from $PQG^{775}\downarrow{}^{776}$LAG to $PPG^{775}\downarrow{}^{776}$MPG. The Jaffa mutation does not influence aggrecanase cleavage at sites in the chondroitin sulphate-rich region of aggrecan. In contrast, blocking cleavage at the primary collagenase cleavage site prevents secondary and subsequent cleavage events in Bailey type II collagen. Juniper mice are resistant to both aggrecanases and collagenases

Methods: Aggrecan released into the medium from Wildtype, Bailey, Jaffa and Juniper femoral head cartilage explants (n= 5-6 per genotype), treated for 3 days ± IL-1, was measured by the DMMB assay. Cartilage used in the explant experiments was homozygous for all genotypes. We used the DMM surgical model of OA to compare tibial cartilage erosion in Wildtype, Bailey, Jaffa and Juniper mice at 8-weeks post-surgery. Morphological joint abnormalities in homozygous Bailey precluded their use in arthritis studies. Accordingly, the in vivo comparisons were made between heterozygous Bailey, homozygous Jaffa and Juniper mice that were heterozygous for the Bailey mutation and homozygous for the Jaffa mutation. Sagittal sections collected at 40μm intervals through the medial compartment of the knee were scored for aggrecan loss and cartilage erosion by two independent scorers blinded to the genotype. The data were analysed by the Mann-Whitney U-test

Results: Aggrecan loss from explants treated with IL-1α was significantly reduced in all mutant genotypes compared with Wildtype. Juniper explants lost the least amount of aggrecan. The hierarchy of aggrecan loss was Wildtype > Jaffa > Bailey > Juniper samples. Aggrecan loss from explants treated with retinoic acid was also significantly reduced in all mutant genotypes compared with wildtype; again Juniper explants lost the least amount of aggrecan. However, with retinoic acid treatment, the hierarchy of aggrecan loss was Wildtype > Bailey > Jaffa > Juniper samples. We measured aggrecan loss and cartilage erosion 8-weeks after DMM surgery and as predicted, found that both aggrecan loss and tibial cartilage erosion were significantly reduced in Juniper compared with Wildtype. For aggrecan loss, whereas there was no protection in Jaffa compared with Wildtype at 8 weeks, the aggrecan loss from Bailey was significantly less than for Wildtype. For cartilage erosion, both Bailey and Jaffa were protected compared with Wildtype at 8 weeks. Similarly, Juniper was better protected against cartilage erosion than either Jaffa or Bailey

Conclusions: Mutations that partially block collagenolysis (heterozygous Bailey) and aggrecanolysis (homozygous Jaffa for the IGD site only) protect against cartilage erosion in experimental OA. Furthermore, protecting collagen II against collagenase attack is equal to, or better than, protecting aggrecan against IGD aggrecanase cleavage, in terms of cartilage erosion and aggrecan loss respectively (see Figure)

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S100A8 AND S100A9 ACT AS 'PRIMERS' OF A CATABOLIC RESPONSE IN CHONDROCYTES BUT ADDITIONAL SIGNALS ARE REQUIRED TO ACTIVATE CARTILAGE DEGRADATION

A. van Hummel [1,2], C. Little [2], T. Vogl [3], J. Roth [3], H. Zreiqat [1]. [1] *Tissue Engineering and Biomaterials Unit, Faculty of Engineering, The Univ. of Sydney, Sydney, Australia;* [2] *Raymond Purves Bone & Joint Res. Lab., The Kolling Inst. Of Med. Res., Univ. of Sydney, Royal North Shore Hosp., Sydney, Australia;* [3] *Inst. of Immunology, Univ. of Muenster, Muenster, Germany*

Purpose: Calcium binding proteins S100A8 and S100A9 are increased in cartilage in acute and chronic inflammatory arthritis; however their role in osteoarthritis (OA) is less clear. Chondrocyte *S100A8* and *S100A9* mRNA are increased during the onset of surgically induced murine OA, but both are significantly downregulated as OA progresses. Interestingly, recent studies have shown that cartilage in $S100A9^{-/-}$ deficient mice is protected from degradation in joint instability accompanied by significant synovitis (collagenase-induced-) but not surgically-induced-OA. Whether this is due to more persistent expression of S100A8 and/or A9 or release of additional co-factors from the inflamed synovium in the collagenase model is unclear. S100A8 and S100A9, but not the heterodimer (S100A8/A9) rapidly induce MMP and ADAMTS mRNA expression in chondrocytes, but whether this leads to actual cartilage matrix breakdown has not been resolved. The aim of this study was to determine whether S100A8 or S100A9 alone or in combination with IL-1 can activate MMPs and aggrecanases with resultant chondrolysis and whether this is time-dependent.

Methods: Normal ovine articular cartilage explants were cultured for 1, 2, 4, 7 or 14 days in serum-free media ± 10^{-7}M human S100A8, S100A9 or S100A8/A9, with or without 10ng/ml IL-1α (n=6/treatment). Gene expression of *S100A8*, *S100A9*, key cartilage proteins, metalloproteinases and their inhibitors was measured using qRT-PCR. Collagen and aggrecan release were measured as hydroxyproline and glycosaminoglycan respectively. Media MMP-2 and MMP-9 activity were evaluated by gelatin zymography and MMP-13 using a fluorometric assay.

Results: S100A8 and S100A9 alone significantly ($p<0.05$) up-regulated *MMP1*, *MMP3*, *S100A9*, *ADAMTS5* and *MMP13* mRNA throughout the